Medical and Pediatric Oncology 27:529–533 (1996)

Secondary Central Nervous System Metastases in Children With Neuroblastoma

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Cerebral and meningeal involvement in patients with primary extracranial neuroblastoma (NB) is unusual although it is generally present in disseminated disease. The intensification of chemotherapy that has prolonged survival in these children has changed the pattern of relapse presentation, as occurs with isolated central nervous system (CNS) disease. We report 4 patients with secondary CNS metastases. Three infants of 16, 14, and 10 months of age, diagnosed with primary abdominal NB stage 4, presented neuromeningeal metastases during maintenance chemotherapy with seizures and cranial hypertension as the first manifestation. Another 8-year-old patient diagnosed with NB stage 3 presented local relapse with later neuromeningeal metastases. All died in the following 3 months. The possibility of CNS relapse in patients with NB should be considered when neurological symptoms and signs appear. These new relapse forms overshadow the prognosis of these children.

Key words: neuroblastoma, nervous system neoplasms, brain metastases, child

INTRODUCTION

Neuroblastoma (NB) is a malignant tumor that originates in the neural crest cells and represents the most frequent extracranial solid mass in childhood. Usually NB is localized in the abdomen (adrenal glands or paraspinal retroperitoneal space) [1]. The tumor spreads locally or through the lymphatic or hematogenous pathway and approximately 60% of these children have disseminated stage 4 at diagnosis [2]. The metastases are usually found in the lymphatic nodes, bone marrow, liver, and bones and are rare in the lungs, cerebral parenchyma, or leptomeninges [3].

Prognosis of children with stage 4 NB depends on several factors such as age, tumor extension, localization, histology, serum levels of ferritin, neuron-specific enolase (NSE), lactate dehydrogenase (LDH), and urinary excretion of catecholamines; in addition, amplification of N-myc, DNA cell content, and cytogenetic abnormalities in chromosome 1 in the tumoral tissue are now important prognosis factors [4–6].

The combination of surgery, radiotherapy, and chemotherapy in the treatment of this tumor has improved the remission rate and survival in these patients [7–11]. Nevertheless, long-term disease-free survival in stage 4 NB of children older than 1 year remains poor (less than 30% in most of the series including megatherapy and bone marrow transplantation) [12,13]. Late relapses also remain a problem [14]. In recent years, the intensification of treatment and longer survival have contributed to new forms of relapse such as cerebromeningeal metastases even at isolated localizations [15–17].

We report 4 patients with CNS metastases of NB, in which 3 of them had solitary relapse.

PATIENTS AND METHODS

Case 1

Case 1 was a 14-month-old male with a 1-month history of weight loss, otorrhea, and right supraorbitary swelling. In addition, left proptosis, hepatomegaly, and a right abdominal mass was found on physical examination. Ultrasound (US) and computed tomography (CT) revealed a mass with calcifications in the right adrenal area and retroperitoneal node involvement. Metaiodobenzylguanidine-I123 (MIBG-I123) was positive in right renal fossa with several bone metastases also found on technetium (Tc)-bone scan. Bone marrow was infiltrated by NB cells. In the cranial CT the orbits, ethmoid, sphenoid bones, and left temporal lobe were infiltrated by tumor. The cerebrospinal fluid (CSF) cytology was negative for blasts. The patient was staged as NB-4 and treated with a national protocol. Complete clinicoradiological response was obtained but second-look surgery revealed microscopic rests and he was treated with radiotherapy (20 Gy tumoral bed) and polychemotherapy as continuation. After 16 months of follow-up, he suddenly had seizures and fell into a coma with residual right hemisyndrome without radiological findings on CT, magnetic resonance (MR), and arteriography. MIBG-I123 was positive locally and in the parieto-occipital region. CT scan 1 month later revealed contrast enhancement in the occipital area and

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Received August 22, 1995; accepted December 18, 1995.

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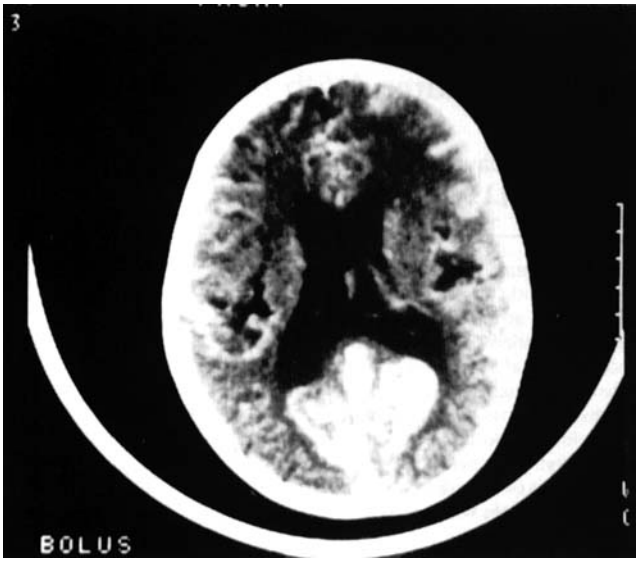

Fig. 1. Case 1. head scan shows large partially enhancing contrast tumor involving the occipital region; leptomeningeal affectation; and hydrocephalus.

Fig. 3. Case 2. MR image at relapse demonstrates hydrocephaly and meningeal gadolinium enhancement.

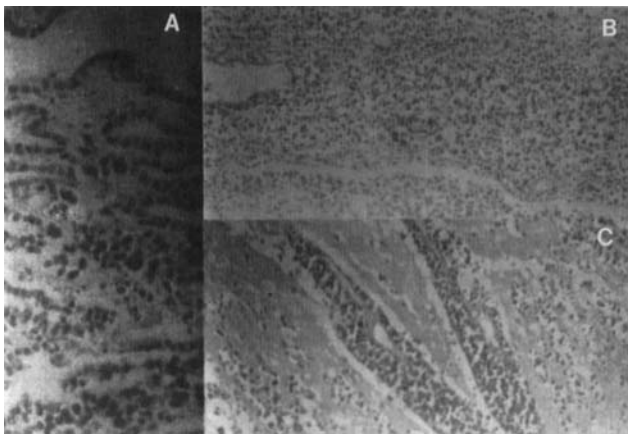

Fig. 2. Case 1. CNS autopsy findings: (**A**) choroid plexus infiltration by tumoral cells; (**B**) meningeal infiltration; and (**C**) Virchow-Robin spaces infiltration.

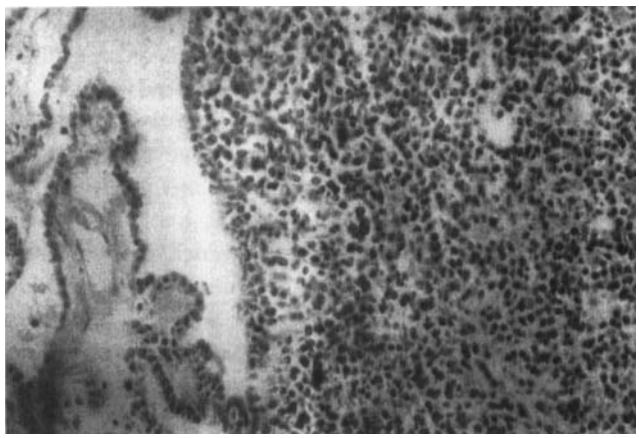

Fig. 4. Case 2. NB metastases in the choroid plexus of the lateral ventricles.

leptomeninges with hydrocephalus (Fig. 1). The child had disease progression and died in 3 months in spite of chemotherapy with platinum derivatives and epipodophyllotoxins. Autopsy findings included tumor in the right adrenal region, retroperitoneal nodes, lungs, liver, bones, and brain (meningeal, Virchow-Robin spaces, and parenchymatous infiltration) (Fig. 2).

Case 2

Case 2 was a 10-month-old female with fever, irritability, anorexia, weight loss for 1 month, hepatomegaly, and abdominal mass. On abdominal US and CT a right adrenal mass, a left adrenal mass, and retroperitoneal nodes were found. MIBG-I123 was positive in both adrenal glands, liver, and bones (femur, sacroiliac, and lumbar columm). Bone marrow was infiltrated. Chest and cranial CT were normal. Staged as NB-4 with bilateral primary, she was treated with the same protocol and obtained complete clinicoradiological-pathological remission. After 16 months of follow-up, she had a seizure with positive spinal tap for blast cells. CT-brain scan and MR revealed meningeal infiltration with hydrocephaly (Fig. 3). She died with status 20 days later. Autopsy revealed massive infiltration of the CNS without evidence of tumor elsewhere (Fig. 4).

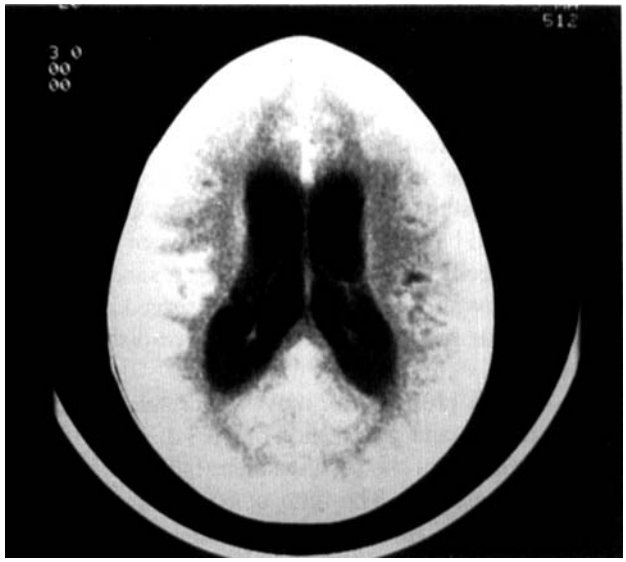

Fig. 5. Case 3. CT scan shows multiple areas of bright contrast enhancing tumor.

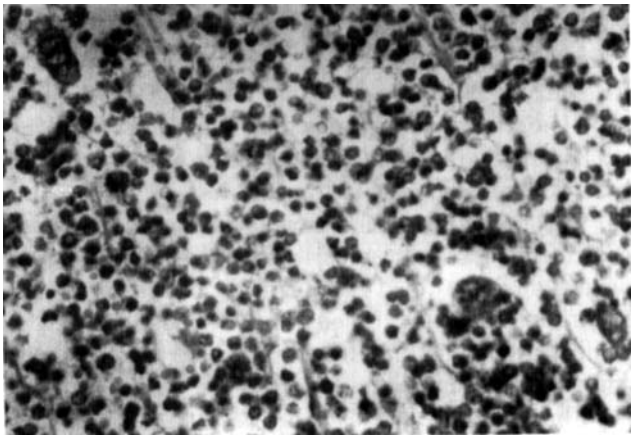

Fig. 6. Case 3. NB metastases in the cerebral parenchyma.

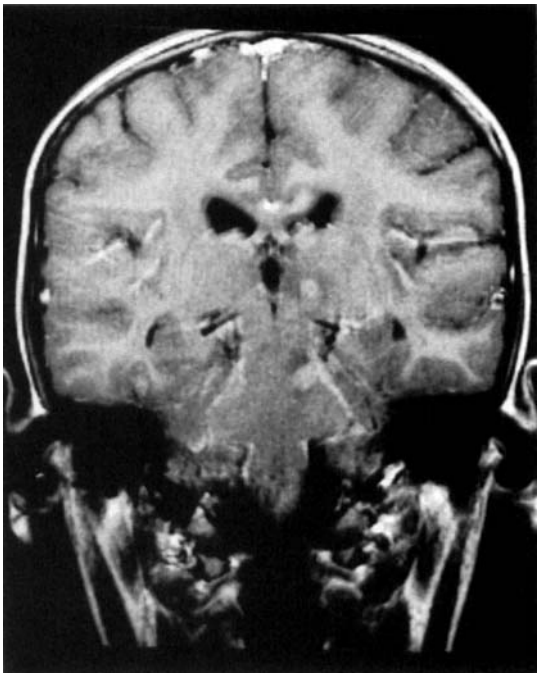

Fig. 7. Case 4. MR showing supratentorial and infratentorial parenchymatous and leptomeningeal tumoral infiltration.

Case 3

Case 3 was a 16-month-old female with fever, anorexia, and bilateral proptosis for approximately 1 month. A right abdominal mass (confirmed on US and CT) and hepatomegaly were found. Bone lytic lesions were present in diploe and orbits on cranial CT. MIBG-I123 confirmed positive isotopic uptake in the right adrenal, ribs, and cranium and was also seen on Tc-bone scan. CSF was negative. Bone marrow was infiltrated by NB cells. The patient was staged and treated as NB-4. She had remission with microscopic residue. Local radiotherapy and polychemotherapy were given. At 9 months of follow-up, without any evidence of disease, she showed symptoms of increased intracranial pressure and seizures and died 12 days later. Obstructive hydrocephalus and parietal infiltrates were found on cranial CT and MR (Fig. 5) and also blasts in CSF. Necropsy limited to the brain revealed infiltration by tumor in the right parietotemporal lobes, meninges, and Virchow-Robin spaces (Fig. 6).

Case 4

Case 4 was an 8-year-old male with cough, respiratory distress, and dorsolumbar pain for 48 hr. A right posterior mediastinum calcified mass that eroded the adjacent ribs and vertebrae was seen on X-ray and CT. Retroperitoneal nodes were seen on US and CT examinations. Serum and urinary markers, bone marrow, and Tc-bone scan were normal. A thoracic mass was completely excised and confirmed NB. The patient was treated for 2 years and continuous complete remission was obtained and maintained for 25 months after all therapy had been stopped. Then he showed radiological evidence of thoracoabdominal relapse and it was confirmed by removal of a right retroperitoneal mass. He was treated with local radiotherapy and chemotherapy for 16 months and obtained complete remission. He complained of headache and sporadic vomiting around the end of treatment but, cranial CT and gadolinium MR were negative for tumor. Due to the persistence of sporadic neurological symptoms, 1 month later the tests were repeated and CSF blasts were found and MR revealed several leptomeningeal and parenchymatous infiltrates (Fig. 7). He was treated again with chemotherapy (IFO, VP16), but died 10 days after CNS involvement was established. Postmortem examination was not done.

DISCUSSION

Intracranial metastases are frequent in patients with disseminated NB and are usually localized in the orbits, cranial bones, venous sinus, and dura mater. Cerebral and meningeal involvement is rare and is associated with direct tumoral extension from bone, dura, or venous sinus [3]. The concept of neuromeningeal metastases refers to incracranial or intraspinal lesions that affect cerebral parenchyma confirmed histologically or diffuse meningeal infiltration with NB cells on CSF smear [15]. In this fashion, lesions derived from bone, dura mater, venous sinus, or orbits are excluded.

Diffuse leptomeningeal dissemination occurs with progression of disease and is a relatively frequent finding in autopsy [3]. Nevertheless, parenchymatous metastases without cranial or dural involvement are rare and only 11 cases were reported before 1980 [17,18]. Since then, the number of cases published are increasing [19–22]. Rohrlich et al. [15] reported 7 patients of 258 NB patients treated at Institute Gustave-Roussy and correlated the presence of cranial and orbitary metastases at diagnosis with CNS relapse. Kellie et al. [16] described 8 cases of CNS relapse from 160 NB patients treated at St. Jude's Children Hospital. Shaw and Eden [17] reported the results of the European Neuroblastoma Study Group (ENSG) which included a register of 950 cases from 1982 to 1989 in which 44 patients had cranial disease (11 intracranial, 1 extradural, and 10 parenchymatous).

Of a small series of 12 children diagnosed and treated for NB at Hospital of Cruces from 1987 to 1990 with the same protocol [11], we observed the appearance of CNS metastases in 4 of them. In 3 cases the neurological symptoms and signs were the first announcement of relapse and for the other patient it happened as a second relapse. The neurological findings were isolated in the latter 3 patients without any evidence of tumor elsewhere. We think that the presence of extensive meningeal infiltration in all of the cases, with abnormalities of cerebral parenchyma in 3 of them, is remarkable. The necropsy done on the first 3 patients was confirmatory of tumoral infiltration in parenchyma and meninges and, although autopsy was not done on the last child, the radiological and cytological findings support the tumoral infiltration of the CNS structures. None of the cases, including the first patient with disseminated disease, had proven direct tumoral extension to the CNS.

The pathway for neuroaxis dissemination by NB cells is not clear and several hypotheses have been postulated. According to De la Monte et al. [3], in some published cases this way may be through CSF spread with extensive leptomeningeal compromise and positive CSF cytology and other cases may be through arterial spread preceded by pulmonary metastases. Although in the 4 patients reported in this paper the pathway is unknown, the important infiltration observed in meninges and Virchow-Robin spaces found at autopsy is striking and could suggest that this dissemination was through the CSF. Positive CSF cytology in cases 2–4 also supports this hypothesis. The association of lung, liver, and bone metastases with deep cerebral parenchymal involvement in case 1 could not exclude the hematogenous pathway. One of the hypotheses postulates that the hematogenous spread to the CNS could be present at the beginning of the disease and tumoral cells could remain there as a sanctuary [16] as in patients with ALL. The 3 cases observed in younger patients in our report presented extensive disease at diagnosis.

The clinical presentation may be variable depending on the extension and localization of CNS disease [15–21]. In 3 of our children the seizures were hard to control by anticonvulsive drugs. The time of relapse in the first 3 cases was 16, 16, and 9 months (mean 13.6), similar to the interval found by Rohrlich et al. [15] and Kellie et al. [16].

Once the CNS relapse is present, clinical progression is usually fast, leading to exitus within 3 weeks in 3 of our children as we observed in previous series [15–17]. The use of platinum derivatives and epipodophyllotoxins delayed the progression to 3 months in case 1. Perhaps this rapid fatal outcome in our patients could be explained by the great extension of CNS involvement. Although the treatment may control the tumor progression temporarily and prolong survival of cases with localized CNS metastases [15–17,23,24], only one case treated with IFO and VP16 has been published as a complete continuous remission during 14 months of follow-up [23].

The appearance of neurological signs and symptoms in a patient with NB should alert one to neuromeningeal relapse although it may also be due to other causes [24]. Regular follow-up by imaging techniques in these children is not as valuable as one might think because they can be normal in patients with CNS disease, as shown in cases 1 and 4 and in other reports [18].

Longer survival obtained by intensified therapy including bone marrow transplant [3,15,17,25] in patients with disseminated NB has led to new forms of relapse presentation in these children. As previously reported in patients with acute lymphoblastic leukemia who need localized treatment over the CNS sanctuary, probably in NB the prolongation of remission with the treatment gives a greater opportunity for the sanctuary sites to become evident and indicates the need for specific treatment over CNS. Fatal prognosis and evolution of patients with CNS infiltrates, no matter the treatments used so far, should prompt us to the necessity of designing new therapeutic protocols to prevent them.

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